Sleep Medicine Reviews xxx (2014) 1–16

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials

Ingrid Jullian-Desayes [a, b], Marie Joyeux-Faure [a, b], Renaud Tamisier [a, b], Sandrine Launois [a, b], Anne-Laure Borel [a, c], Patrick Levy [a, b], Jean-Louis Pepin [a, b, *]

[a] Université Grenoble Alpes, HP2, Inserm U1042, Grenoble, France
[b] CHU de Grenoble, Laboratoire EFCR, Secteur Physiologie Sommeil et Exercice, Pole Thorax et Vaisseaux Grenoble, France
[c] CHU de Grenoble, Département d'Endocrinologie Diabétologie – Maladies de la Nutrition, Pôle Digidune, Grenoble, France

ARTICLE INFO

Article history:
Received 21 May 2014
Received in revised form
9 July 2014
Accepted 12 July 2014
Available online xxx

Keywords:
Obstructive sleep apnea
Cardiometabolic biomarkers
Continuous positive airway pressure
Randomized controlled trial

SUMMARY

Reducing cardiometabolic risk may represent an important target for effective obstructive sleep apnea (OSA) treatment. The impact of continuous positive airway pressure (CPAP), the first line therapy of OSA, on metabolic or inflammatory markers is still debated. A systematic literature search using several databases was performed. We provide a systematic analysis of randomized studies comparing therapeutic versus sham CPAP intervention and also include studies using a CPAP withdrawal design. We addressed the impact of CPAP on the following cardiometabolic biomarkers: 1) plasma and urine catecholamines and their metabolites that reflect sympathetic activity; 2) insulin resistance and lipid metabolism biomarkers; 3) oxidative stress, systemic and vascular inflammation biomarkers; 4) liver enzymes highlighting the association between OSA and nonalcoholic fatty liver disease (NAFLD); 5) coagulation biomarkers. The impact of CPAP on sympathetic activity is robust across studies and occurs rapidly. In contrast to sympathetic activity, the well-designed studies included in this review failed to demonstrate that CPAP alters metabolic or inflammatory markers in OSA. CPAP did not change glucose, lipids, insulin resistance levels or the ratio of patients with metabolic syndrome. In unselected OSA patients, it is not realistic to expect a clinically relevant decrease in cardiometabolic biomarkers with CPAP therapy.

Introduction

Obstructive sleep apnea (OSA) is a common clinical condition characterized by repeated episodes of apnea and hypopnea during sleep. Sleep fragmentation and chronic intermittent hypoxia (CIH) induce intermediate mechanisms such as activation of the sympathetic nervous system [1], oxidative stress and systemic inflammation, responsible for cardiometabolic consequences [2,3] (Fig. 1). OSA is linked with hypertension, arrhythmia, stroke, coronary heart disease, and increased cardiovascular mortality [4]. In addition, OSA is also highly prevalent in patients with metabolic diseases including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD) [5] and is linked to several features of metabolic syndrome among them hypertension, insulin resistance (IR), abdominal obesity and dyslipidemia [6,7]. The effective treatment of OSA may thus represent an important target for reducing cardiometabolic risk. However, the impact of continuous positive airway pressure (CPAP), the first line therapy of OSA, on metabolic or inflammatory markers is still debated [8].

Although the effects of CPAP on various biomarkers have been investigated in hundreds of open clinical studies, the real effects of CPAP on cardiometabolic biomarkers are conflicting mainly owing to different study designs and the presence of major confounders. This review is a systematic analysis of randomized studies comparing therapeutic versus sham CPAP intervention and also includes studies using a CPAP withdrawal design [9,10].

To take account of the intermediary mechanisms involved in OSA pathophysiology (Fig. 1), we will address the impact of CPAP on the following cardiometabolic biomarkers: 1) plasma and urine catecholamines and their metabolites that reflect sympathetic activity; 2) insulin resistance and lipid metabolism biomarkers; 3) oxidative stress, systemic and vascular inflammation biomarkers; 4) liver enzymes highlighting the association between OSA and NAFLD; 5) coagulation biomarkers.

* Corresponding author. Laboratoire EFCR, CHU de Grenoble, CS 10 217, 38043 Grenoble Cedex 9, France.
E-mail address: JPepin@chu-grenoble.fr (J.-L. Pepin).

http://dx.doi.org/10.1016/j.smrv.2014.07.004
1087-0792/

Abbreviations

AHI	apnea–hypopnea index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CIH	chronic intermittent hypoxia
Cox	cyclooxygenase
CPAP	continuous positive airway pressure
CPCs	circulating progenitor cells
CRP	C-reactive protein
CVD	cardiovascular diseases
EMPs	endothelium-derived microparticles
eNOS	endothelial nitric oxide synthase
GMPs	granulocyte-derived microparticles
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment insulin resistance
IH	intermittent hypoxia
IL	interleukin
IR	insulin resistance
LDL	low-density lipoprotein
LMPs	leukocyte-derived microparticles
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NE	norepinephrine
NO	nitric oxide
NOx	total nitrate and nitrite
OSA	obstructive sleep apnea
ODI	oxygen desaturation index
PMPs	platelet-derived microparticles
RCT	randomized controlled trial
T2DM	type 2 diabetes mellitus
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
VLDL	very low-density lipoprotein
vWF	von Willebrand factor

Literature search strategy

We selected only randomized sham-controlled trials i.e., with sham CPAP as the control, addressing the impact of CPAP on cardiometabolic biomarkers. An electronic literature search using the Medline medical research database was conducted. We looked for sham-controlled studies and investigating the effects of CPAP on blood and urinary cardiometabolic biomarkers. First, we used "sham CPAP" as the keyword, then the following keyword associations were used: "subtherapeutic CPAP" AND "randomized trial", "placebo CPAP" AND "randomized trial" and finally "CPAP" AND "randomized trial". We repeated searches until no additional articles could be identified. No language restriction was imposed. For inclusion in the review, a study had to fulfill the following criteria: 1) randomized trial using therapeutic versus sham CPAP 2) urinary or plasma biomarker measurements before and after the intervention.

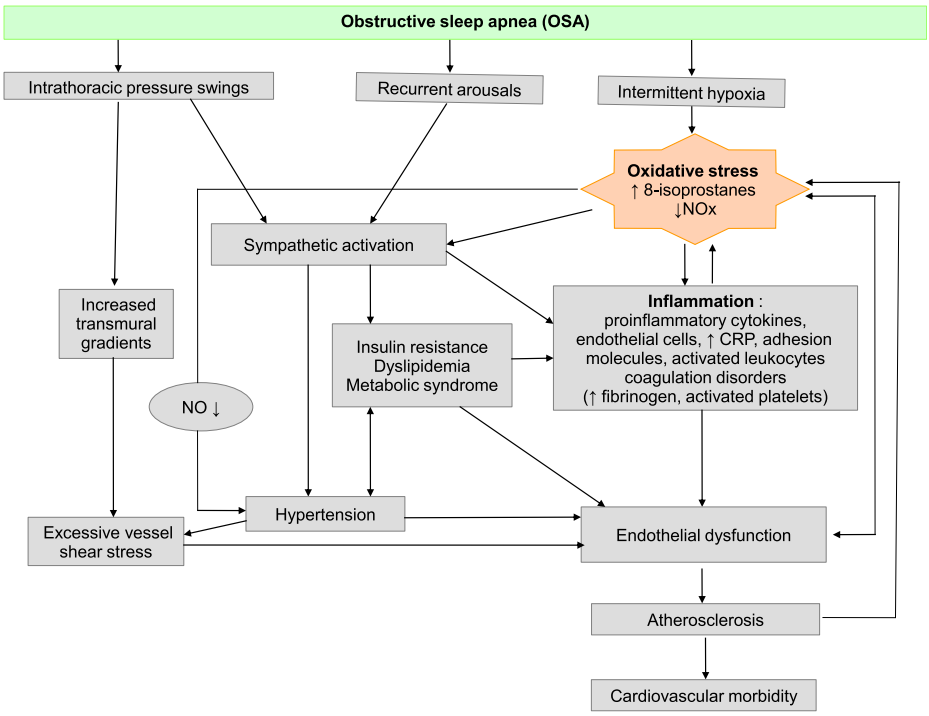

Fig. 1. Obstructive sleep apnea and its cardiometabolic consequences. Adapted from Kohler et al., 2010 [1] and Lavie et al., 2009 [2]. Intermittent hypoxia, one of the consequences of OSA, leads to an increase in oxidative stress that plays a key role in OSA and the development of associated cardiometabolic morbidities. A series of intricate interactions between various transduction pathways promote oxidative stress and inflammation. Enhanced oxidative stress induces inflammation, and then increased proinflammatory cytokines, adhesion molecules and procoagulant activities in turn exacerbate oxidative stress. This vicious circle leads to cardiovascular morbidity. Moreover, sympathetic overactivity and the decrease in NO induced by oxidative stress lead to hypertension. Both hypertension and inflammation promote endothelial dysfunction responsible for atherosclerosis. Finally, this endothelial dysfunction and atherosclerosis can exacerbate oxidative stress [2]. Furthermore, intrathoracic pressure swings and the increase in transmural pressure gradients over vessel walls also probably result in endothelial dysfunction. This is in addition to arousals that seem to activate the sympathetic nervous system and thus also cause endothelial dysfunction. The increased production of catecholamines will also be responsible for rises in blood pressure and sustained blood pressure elevation [1].
CRP: C-reactive protein; IH: intermittent hypoxia; NO: nitric oxide; NOx: total nitrate and nitrite; OSA: obstructive sleep apnea.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

As a result, we identified 76 randomized studies. Among them only 24 studies were sham-controlled and evaluated the changes in biomarker levels after CPAP treatment (Fig. 2). The characteristics of these studies are described in Table 1.

Plasma and urine catecholamines and their metabolites

Background: sympathetic activation and intermittent hypoxia

Oxidative stress and inflammation induced by OSA promote activation of the sympathetic nervous system and then endothelial dysfunction, arterial stiffness and atherosclerosis [2,11,12]. As shown in Fig. 1, oxidative stress induces inflammation, while inflammation in turn promotes oxidative stress. This vicious circle results in sympathetic activation and endothelial dysfunction leading to atherosclerosis. Impaired arterial vasodilating capacity may contribute to hypertension and vascular diseases. Arterial stiffness and atherosclerosis which are associated with OSA are both predictors of long term adverse cardiovascular events. Indeed, prospective studies have reported a higher prevalence of hypertension, incident coronary heart disease, stroke and heart failure in OSA compared to well-matched control groups [4]. One of the main underlying mechanisms responsible for these associations is the sympathetic overactivity induced by OSA. Independently of confounders such as obesity or its comorbidities, young and lean healthy humans exposed to one or two weeks of nocturnal intermittent hypoxia (IH) increased their muscle sympathetic nervous activity and a decline in the baroreflex control of sympathetic outflow was observed [13]. They simultaneously increased their hypoxic and hypercapnic ventilatory responses supporting the role of an augmentation in carotid chemoreflex function in inducing sympathetic overactivity. Moreover, increased sympathetic outflow to the kidney stimulates renin release and leads to an elevation of angiotensin II and aldosterone levels highlighting the renin-angiotensin system's role in OSA induced hypertension [14].

Summary of data from open studies

Historically, the majority of open studies suggested that CPAP decreases the levels of plasma and urine catecholamines. In severe OSA patients, long-term CPAP treatment can reduce levels of markers of sympathetic activity including plasma norepinephrine (NE) and daytime and nighttime urinary metabolites (vanylmandelic acid and metanephrines) [15]. A reduction in blood pressure (BP) and heart rate, in addition to a decrease in plasma NE levels during sleep but also during daytime, has been shown in hypertensive OSA patients treated by CPAP [16]. Thus, CPAP seems to have an impact on sympathetic activity not only at night, but also beyond the hours of sleep. Moreover, even short exposure to CPAP treatment seems sufficient to decrease urinary NE levels and BP in patients with severe OSA [17].

Data from randomized sham-controlled studies: is CPAP treatment able to decrease sympathetic activity?

Eight randomized trials have measured catecholamines or their metabolites pre- and post-treatment either with therapeutic or sham CPAP. However, it should be noted that in these studies catecholamines and metabolites were mainly assessed as secondary outcomes (Table 2). Randomized trials that included non-OSA control groups at baseline report higher nocturnal NE and epinephrine levels in OSA patients compared to controls [18,19]. Also, Ziegler et al. [20] reported that the number of apneas and the severity of nocturnal hypoxia were significantly correlated with daytime urinary NE levels. Moreover, daytime plasma NE levels were correlated with the patient's respiratory disturbance index.

Concerning the effect of CPAP on catecholamine levels, five of the eight randomized controlled trials (RCTs) confirmed a significant reduction of sympathetic activity using one or more biomarkers. First, Ziegler et al. [20] described a significant reduction of daytime sympathetic activation, but the nighttime reduction of sympathetic activity failed to attain statistical significance after short-term CPAP treatment (10 d). Furthermore, therapeutic CPAP decreased urinary and plasma NE levels together with a parallel reduction in blood pressure and restored function to desensitized β-adrenergic receptors [20]. This is a contributive finding as untreated OSA patients exhibit a desensitization of the alpha and beta 2-adrenergic receptors linked with endothelial dysfunction [21]. The study by Lam et al. [22] is the only one with a parallel design that did not show a significant change in urinary epinephrine and NE levels after short-term CPAP treatment (one week). In 2011, the most recent RCT we found [23] with sham CPAP as a placebo that measured catecholamine levels, reported no effect of CPAP on epinephrine and a decrease in 24 h and awake NE. In two RCTs urinary catecholamine metabolites were also used to evaluate the activity of the sympathetic nervous system. Kohler et al. [24] observed a significant reduction in 24-h normetanephrine excretion of 26%, compared with a non-significant increase in the sham CPAP group. Mills et al. [25] also observed a reduction in plasma NE and daytime/nighttime urine NE excretion. They were the first to

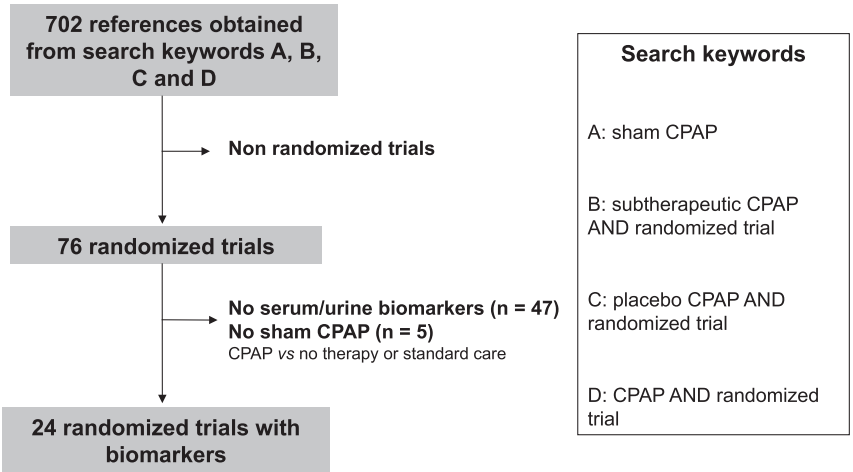

Fig. 2. Flow diagram of articles identified during the study selection process. CPAP: continuous positive airway pressure.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Table 1
Characteristics of studies. AHI: apnea-hypopnea index; BMI: body mass index; BP: blood pressure; CPAP: continuous positive airway pressure; CPCs: circulating progenitor cells; E: epinephrine; ESS: Epworth sleepiness score; HR: heart rate; IR: insulin resistance; MPs: microparticles; NE: norepinephrine; NOx: total nitrite and nitrate; ODI: oxygen desaturation index (ODI 3: ODI, > 3% dips, ODI 4: ODI, >4% dips); OSA: obstructive sleep apnea; PASP: pulmonary arterial systolic pressure; PAT: peripheral arterial tone; PSG: polysomnography; RDI: respiratory disturbance index; T2DM: type 2 diabetes mellitus; VAF: visceral abdominal fat.

Author	Study design Duration of CPAP exposure	Population studied (AHI, ODI, RDI : number of events/hour, BMI : kg/m²)	Sample size and CPAP/Sham CPAP compliance (h/night)	Primary outcome(s)
Alonso Fernandez et al, 2009 [19]	Cross-over 12 weeks No wash-out	Men Middle-aged OSA: AHI ≥ 10, daytime sleepiness (ESS ≥ 11) Mean BMI: 30.5 ± 4.0	Control group (n = 15) OSA (n = 31) 25 randomized **CPAP/ sham CPAP (n = 13)** **sham CPAP/ CPAP (n = 12)** No difference in compliance between arms CPAP: 6.2 ± 1.1 sham CPAP: 6.3 ± 1.6	To compare the concentration of 8-isoprostanes and total nitrate and nitrite (NOx) (OSA vs control) Effects of CPAP on oxidative stress and nitrates
Arias et al, 2006 [26]	Cross-over 12 weeks No wash-out	Predominantly men Middle-aged OSA: AHI ≥ 10 and daytime sleepiness (ESS ≥ 10) Mean BMI: 30.9 ± 4.0	Control (n = 10) 100% men OSA (n = 23) 96% men **sham CPAP/CPAP sequence (n = 11)** **CPAP/sham CPAP sequence (n = 10)** No difference in compliance between arms CPAP: 6.2 ± 1.1 sham CPAP: 5.8 ± 1.4	Compare the levels of pulmonary arterial systolic pressure PASP (OSA *vs* healthy) Effects of CPAP on PASP
Arias et al, 2008 [18]	Cross-over 12 weeks No wash-out	Men OSA: AHI ≥ 10 and daytime sleepiness (ESS > 11) Mean BMI: 30.5 ± 4.0	Control (n = 15) OSA (n = 30) 25 randomized **sham CPAP /CPAP sequence (n = 12)** **CPAP/sham CPAP sequence (n = 13)** No difference in compliance between arms CPAP: 6.2 ± 1.1 sham CPAP: 6.3 ± 1.6	Difference in inflammatory biomarker levels between OSA and control Effects of CPAP on inflammatory biomarkers
Ayers et al, 2013 [10]	Parallel 2 weeks CPAP withdrawal	40 men and 1 woman ODI 4 > 10 without CPAP Treated with CPAP for more than 12 months with an average compliance ≥ 4 h/night Mean BMI: 32.9 ± 6.5 in CPAP group/ 33.1 ± 4.4 in sham CPAP group	n = 41 **CPAP withdrawal (n = 21)** **Continued CPAP (n = 20)** No difference in compliance between arms CPAP: 373.1 ± 67.9 minutes Sham CPAP: 362.8 ± 72.3 minutes	Effect of CPAP withdrawal on levels of MPs
Coughlin et al, 2007 [37]	Cross-over 6 weeks No wash-out	Men OSA: daytime sleepiness (ESS ≥ 10) and AHI > 15 Predominantly obese (mean BMI: 36.1 ± 7.6) No patient with T2DM	n = 35 **CPAP/sham (n = 18)** **sham/CPAP (n = 17)** CPAP compliance > sham CPAP CPAP: 3.9 (0-7.4) sham CPAP: 2.6 (0-7.5)	Effect of CPAP on BP and other features of metabolic syndrome
Hoyos et al, 2012 [40]	Parallel 12 weeks (+ 12 weeks CPAP for all patients in open follow-up)	Men Moderate to severe OSA: AHI ≥ 20 and an ODI 3 ≥ 15 **Without T2DM** Mean BMI: 31.0 ± 5.1 in sham group/ 31.6 ± 5.3 in CPAP group	n = 65 **CPAP (n = 34)** **sham CPAP (n = 31)** No difference in compliance between arms but low mean compliance during blinded period CPAP: 3.6 sham CPAP: 2.8 At 24 weeks: CPAP compliance: 4	Change at 12 weeks from baseline in VAF, ISx (insulin sensitivity) and liver fat
Kohler et al, 2008 [24]	Parallel 4 weeks	Men Moderate to severe OSA: ODI 4 >10 and daytime sleepiness (ESS ≥ 10) Mean BMI: 35.8 ± 7.3 in CPAP group/ 34.5 ± 5.0 in sham CPAP group	n = 102 **CPAP (n = 51)** **sham CPAP (n = 51)** No difference in compliance between arms CPAP: 4.7 ± 2.1 sham CPAP: 3.9 ± 2.5	Effects of CPAP on 24-h urinary catecholamine excretion, baroreflex sensitivity, arterial stiffness and 24-h ambulatory BP
Kohler et al, 2009 [87]	Parallel 4 weeks	Men Moderate to severe OSA: daytime sleepiness (ESS ≥ 10) and ODI 4 > 10 Obese (mean BMI 34.5 ± 5.0 in sham CPAP group/ 35.8 ± 7.3 in CPAP group)	n = 100 **CPAP (n = 51)** **sham CPAP (n = 49)** No difference in compliance between arms CPAP: 4.7 ± 2.1 sham CPAP: 3.9 ± 2.5	Effects of CPAP on inflammatory markers
Kohler et al, 2009 [90]	Parallel 4 weeks	Men Moderate to severe OSA: daytime sleepiness ESS ≥ 10 and ODI 4 > 10 Mean BMI: 34.4 ± 4.6 in sham CPAP group/ 35.6 ± 7.1 in CPAP group	n = 94 **CPAP (n = 47)** **sham CPAP (n = 47)** No difference in compliance between arms CPAP: 4.6 ± 2.1 sham CPAP: 3.9 ± 2.5	Effect of CPAP on liver enzymes
Kohler et al, 2011 [9]	Parallel 2 weeks CPAP withdrawal	40 men and 1 woman ODI 4 > 10 without CPAP Treated with CPAP for more than 12 months with an average compliance ≥ 4 h/night Mean BMI: 32.9 ± 6.5 in CPAP group/ 33.1 ± 4.4 in sham CPAP group	n = 41 **CPAP withdrawal (n = 21)** **Continued CPAP (n = 20)** No difference in compliance between arms CPAP: 373.1 ± 67.9 minutes sham CPAP: 362.8 ± 72.3 minutes	Determine the effects of CPAP withdrawal (PSG, sleepiness, endothelial function, BP, HR, catecholamines, blood markers of systemic inflammation, and metabolism)
Kritikou et al, 2014 [53]	Cross-over 2 months 1 week wash-out	Men and post-menopausal women Middle aged OSA: AHI > 10 for women and > 15 for men **Without T2DM** Non obese (mean BMI: 27.09 ± 2.60 for men and 30.54 ± 3.19 for women)	Control (n = 39) 18 men + 21 women OSA (n = 38) 20 men + 18 women 35 randomized CPAP: 6.1 ± 1.2 sham CPAP: 5.3 ± 1.2 CPAP adherence did not depend on treatment order	Association between OSA and inflammation/IR Effects of CPAP

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Lam et al, 2010 [22]	Parallel 1 week (+ 11 weeks open follow-up for therapeutic CPAP group only)	Men Moderate/severe OSA: AHI ≥ 15 **Without T2DM** Mean BMI: 27.5 ± 3.7	n = 61 **CPAP (n = 31)** **sham CPAP (n = 30)** At 1 week: CPAP compliance > sham CPAP compliance CPAP: 6.2 ± 1.5 sham CPAP: 4.5 ± 2.0 At 12 weeks: CPAP compliance: 4.9 ± 1.4	Impact of CPAP on insulin sensitivity
McEwen et al, 2012 [97]	Cross-over 2 months 1 month wash-out	Predominantly men Severe OSA: AHI ≥ 25 and ODI ≥ 20 Obese (mean BMI: 31.7 ± 4.1)	28 patients 25 men + 3 women CPAP compliance > sham CPAP CPAP: 4.4 ± 2.2 sham CPAP: 3.4 ± 2.3	Effects of CPAP on any diurnal pattern or levels of fibrin generation
Mills et al, 2006 [25]	Parallel 14 days	Men and women OSA: AHI > 15 Mean BMI: 31.7 ± 1.4 in CPAP group/ 32.2 ± 1.7 in sham CPAP group 17/50 hypertensive without antihypertensive drugs	n = 50 **CPAP (n = 17)** 15 men + 2 women 8/17 hypertensive **sham CPAP (n = 16)** 13 men + 3 women 4/16 hypertensive **Nocturnal oxygen therapy (n = 17)** No difference in compliance between arms CPAP: 6.8 ± 0.4 sham CPAP: 6.0 ± 0.3	Is the reduction in NE due to an increase in NE clearance and/or a decrease of NE release rate?
Philips et al, 2011 [23]	Cross-over 2 months 4 weeks wash-out	35 men and 3 women Moderate to severe OSA: AHI ≥ 25 with a significant amount of intermittent hypoxia (ODI 3 ≥ 20) 24/29 patients who completed the study had severe OSA (AHI ≥ 30) Mean BMI: 32.1 ± 4.3	n = 38 (1 excluded) **CPAP/sham CPAP (n = 18)** **sham CPAP/CPAP (n = 19)** CPAP compliance > sham CPAP CPAP: 4.4 ± 2.2 sham CPAP: 3.4 ± 2.3	Effect of CPAP on post-prandial lipidemia (PPL)
Phillips et al, 2012 [98]	Cross-over 2 months 1 month wash-out	25 men + 3 women Upper moderate or severe OSA: AHI ≥ 25 with a hypoxic component ODI ≥ 20 Middle-aged Obese (mean BMI: 31.7 ± 4.1)	n = 37 randomized data available for 28 only CPAP compliance > sham CPAP CPAP: 4.4 ± 2.2 sham CPAP: 3.4 ± 2.3	Improvement in coagulability during both waking and sleeping hours in patients with severe OSA after 2 months of CPAP treatment
Prudon et al, 2013 [52]	Parallel 3 months	Men OSA: ODI 4 > 10 with daytime sleepiness (ESS ≥ 9) **All with stable T2DM** Obese (mean BMI: 35.6 ± 3.6 in sham group/ 36.4 ± 5.0 in CPAP group)	n = 38 **CPAP (n = 19)** **sham CPAP (n = 19)** No difference in compliance between arms CPAP: 3.7 (0-9.1) sham CPAP: 3.7 (0-8.5)	Effects of CPAP on glycemic control and IR
Robinson et al, 2004 [36]	Parallel 1 month	Men OSA: daytime sleepiness (ESS > 9) and ODI 4 > 10 Predominantly obese (mean BMI: 35.9 ± 6.3 in sham group/ 35.6 ± 7.6 in CPAP group) 23/220 hypertensive 2/220 T2DM	n = 220 **CPAP (n = 108)** **sham CPAP (n = 112)** (lipids data available for n = 213) CPAP compliance > sham CPAP CPAP: 5.0 ± 1.9 sham CPAP: 4.1 ± 2.4	Effects of CPAP on circulating markers of cardiometabolic risk
Simpson et al, 2013 [78]	Parallel 12 weeks	Men with moderate-to-severe OSA. AHI ≥ 20 and ODI 3 ≥ 15 Mean BMI: 31.7 ± 6.0 in CPAP group/ 31.1 ± 5.6 in sham CPAP group Without T2DM	n = 46 **CPAP (n = 25)** **sham CPAP (n = 21)** CPAP compliance > sham CPAP CPAP: 3.5 ± 1.9 sham CPAP: 2.2 ± 1.8	Effect of CPAP on endothelial function measured by PAT and CPCs
Sivam et al, 2012 [42]	Cross-over 8 weeks 1 month wash-out	26 men and 1 woman Upper moderate or severe OSA: AHI ≥ 25 with a hypoxic component (ODI ≥ 20) **2 patients with T2DM** Obese (mean BMI: 31.3 ± 3.8)	n = 27 CPAP compliance > sham CPAP CPAP: 4.6 ± 2.0 sham CPAP: 3.4 ± 2.2	Effect of CPAP on adipose tissue distribution
Von Kanel et al, 2013 [94]	Parallel 3 weeks	OSA: AHI ≥ 10 Patients with antihypertensive medications had these completely tapered Mean BMI: 31.4 ± 6.2 in CPAP group/ 29.1 ± 3.9 in sham CPAP group	Control (n = 24) 38% men OSA (n = 51) 92% men **CPAP (n = 25)** **sham CPAP (n = 26)** No difference in compliance between arms: CPAP: 5.7 ± 1.3 sham CPAP: 6.4 ± 1.5	OSA patients' day/night rhythm of several prothrombotic markers and potential changes with CPAP
Weinstock et al, 2012 [54]	Cross-over 8 weeks 1 month wash-out	42% men Moderate to severe OSA (AHI > 15) with **impaired glucose tolerance but no diabetes** 50% with severe OSA (AHI ≥ 30) Morbidly obese (mean BMI: 39 ± 8 in CPAP/sham sequence; 38 ± 8 in sham/CPAP sequence)	n = 50 **CPAP/sham (n = 25)** **sham/CPAP (n = 25)** CPAP compliance > sham CPAP CPAP: 4.8 sham CPAP: 3.4	Effect of CPAP on glucose tolerance
West et al, 2007 [38]	Parallel 3 months	Men OSA: daytime sleepiness (ESS ≥ 9) and ODI 4 > 10 **Stable T2DM** Mean BMI: 36.8 ± 4.6 in sham group/ 36.6 ± 4.9 in CPAP group	n = 42 **CPAP (n = 20)** **sham CPAP (n = 22)** No difference in compliance between arms but overall low compliance CPAP: 3.3 ± 2.6 sham CPAP: 3.5 ± 2.8	Effect of CPAP on glycemic control and IR
Ziegler et al, 2001 [20]	Parallel 10 days	OSA: RDI > 15 Mean BMI: 32.5 ± 1.1 in CPAP group/ 28.7 ± 1.3 in sham CPAP group 11 hypertensive patients without antihypertensive drugs treatment	n = 38 80% men **CPAP (n = 20)** 14 men + 6 women 6/20 hypertensive **sham CPAP (n = 18)** 16 men + 2 women 5/18 hypertensive No difference in compliance (raw data not provided)	Effect of CPAP treatment on sympathetic nervous activity

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Table 2
Effects of CPAP on serum and urine catecholamines and their metabolites. AHI: apnea-hypopnea index; BMI: body mass index; BP: blood pressure; CPAP: continuous positive airway pressure; E: epinephrine; HR: heart rate; IL: interleukin; NE: norepinephrine; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PASP: pulmonary arterial systolic pressure; RDI: respiratory disturbance index; SaO_2: oxygen saturation; sTNFR: soluble tumor necrosis factor receptor; TAG-AUC 24h: area under the 24-hour triglyceride concentration curve.

Author	Biomarkers of sympathetic activation	Main results	Comments
Ziegler et al, 2001 [20]	Daytime and night-time urinary NE excretion Daytime plasma NE	**Decrease by 23% in daytime plasma NE and by 36% in daytime urinary NE** Night-time urinary NE excretion decreased in both groups but no difference between groups	At baseline: The number of apneas and severity of nocturnal hypoxia correlated significantly with daytime urinary NE levels Correlation between daytime plasma NE levels and RDI No correlation of night-time measures with sleep disturbances and hypoxia Groups were not well matched for BMI and urinary NE levels at baseline: CPAP > sham CPAP
Arias et al, 2006 [26]	Nocturnal and diurnal urinary levels of NE, E	No significant changes	At baseline, PASP higher in OSA than in control group Per protocol analysis: 2 patients excluded for average night CPAP usage < 3.5h No intention-to-treat analysis
Mills et al, 2006 [25]	NE clearance, and release rates, circulating NE levels, urinary NE excretion	**Increase in NE clearance** **Decrease in plasma NE levels, and daytime/nighttime NE excretion** NE release rate unchanged	At baseline: AHI related to NE release rate and day and night NE excretion rates BP related to day and night NE excretion Correlation between nocturnal time spent at SaO_2 < 90% and NE release rate, supine plasma NE levels, day and night NE excretion rates
Arias et al, 2008 [18]	Nocturnal and diurnal urinary levels of NE and E	No significant changes	Nocturnal urinary levels of NE and epinephrine significantly higher in OSA patients compared to controls at baseline Nocturnal epinephrine dip significantly greater in control subjects Low epinephrine nocturnal dip associated with higher sTNFR-1 IL-6 levels correlated with diurnal NE levels Per protocol analysis: 5 patients excluded for average night CPAP usage < 3.5h No intention-to-treat analysis
Kohler et al, 2008 [24]	24-h urinary normetanephrine	**Decreased by 26%**	No correlation between changes in mean 24-h BP and those in urinary normetanephrine in the therapeutic CPAP group
Alonso Fernandez et al, 2009 [19]	Nocturnal and diurnal levels of NE, E	No significant changes	Nocturnal levels of NE and epinephrine higher in OSA patients than in control subjects at baseline Per protocol analysis: 2 patients excluded for average night CPAP usage < 3.5h No intention-to-treat analysis
Lam et al, 2010 [22]	Urinary E, NE, metanephrine, normetanephrine collected between 22h and 8h	No changes after 1 week	**Open follow-up study: reduction in urinary E and NE after 12 weeks but only in obese patients (BMI ≥ 25 kg/m², Asian patients with above this value are considered as obese) (subgroup analysis)**
Philips et al, 2011 [23]	24 h, awake and asleep urinary E and NE	**24 h and awake NE decreased** No changes on E and asleep NE	Per protocol analysis: exclusion of patients with average night CPAP usage < 4.5h Intention-to-treat analysis for TAG-AUC_{24} only but results not shown No treatment order effect
Kohler et al, 2011 [9]	Urinary NE and E from 7:00 pm to 7:00 am	**CPAP withdrawal associated with an increase in overnight urine NE compared to CPAP group** but not in E	At 2 weeks: CPAP withdrawal associated with significant: - increase in AHI, ODI, and number of arousals - decrease in endothelial function - increase in morning systolic BP, morning diastolic BP, and morning HR whereas there was no increase in markers of systemic inflammation, insulin resistance, or blood lipids

Table 3
Effects of CPAP on lipid metabolism biomarkers. AHI: apnea-hypopnea index; Apo B: apolipoprotein B; CPAP: continuous positive airway pressure; FFA: free fatty acids; HDL: high density lipoprotein; LDL: low density lipoprotein (calculated with Friedwald equation); ODI: oxygen desaturation index; PPL: post-prandial lipidemia; TAG-AUC 24h: area under the 24-hour triglyceride concentration curve; TG: triglycerides.

Author	Biomarkers of lipid metabolism	Main results	Comments
Robinson et al, 2004 [36]	Total cholesterol and TG	No change in TG **Significant fall in total cholesterol with therapeutic CPAP but difference between the 2 groups showed only a trend towards significance**	Values within normal laboratory ranges at baseline for total cholesterol, and triglyceride Short duration of treatment Blood samples were taken in the non-fasting state for TG
Coughlin et al, 2007 [37]	Total, LDL and HDL cholesterol TG	No changes in percentage of patients exhibiting metabolic syndrome	Better compliance with placebo therapy during the second treatment limb may reflect a carry-over effect Intention-to-treat analysis and per-protocol analysis (exclusion of patients with CPAP compliance < 3.5 h/night)
West et al, 2007 [38]	Total and HDL cholesterol TG	No change in metabolic parameters	Per protocol analysis involving only good compliers did not change the results
Lam et al, 2010 [22]	Total, LDL and HDL cholesterol TG Apo B	No changes in LDL and HDL cholesterol in the randomized phase of the study	**Decrease in total cholesterol, TG and apoB after 12 weeks, blinded + open phases of the study**
Philips et al, 2011 [23]	PPL determined from the TAG-AUC_{24} Total, HDL and non HDL cholesterol FFA	**Decrease in PPL (TAG-AUC_{24}) also in intention-to-treat analysis** TG levels peaked twice at 2:00 p.m and at 3:00 a.m in both CPAP and placebo group. **Both peaks decreased more under therapeutic CPAP than sham CPAP** **Decrease in mean 24-hour total cholesterol, HDL and non-HDL cholesterol with CPAP** No change on FFA	No treatment order effect Standardized food intake at fixed time Per-protocol analysis (CPAP use ≥ 4.5h/night) + Intention-to-treat analysis for TAG-AUC_{24} only
Kohler et al, 2011 [9]	Cholesterol, HDL, LDL	No changes in cholesterol after CPAP withdrawal compared to CPAP group.	At 2 weeks: CPAP withdrawal associated with significant: - increase in AHI, ODI, and number of arousals - decrease in endothelial function

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

assess NE kinetics, and found that CPAP induced an increase in NE clearance whereas the NE release rate was unchanged.

In three studies [18,19,26] out of the eight RCTs, no effect of CPAP on urinary catecholamines was observed despite CPAP treatment lasting three months. The absence of any effect cannot be explained by poor compliance to CPAP, since the mean compliance value was over 6 h/night. However, these three trials used a cross-over design and did not include a wash-out period, such that a potential carry-over effect could pose a major limitation.

Finally, the beneficial effect of CPAP on sympathetic activity seems to be robust across well designed studies and occurs rapidly since two trials with a very short duration of treatment (10–14 d) nevertheless showed a significant decrease in plasma NE levels [20,25]. Kohler et al. [9] have developed a CPAP withdrawal model which rapidly reintroduces OSA characteristics and is a useful addition to classical study paradigms investigating the physiological consequences of OSA. Accordingly, with classical sham CPAP RCTs, two weeks of CPAP withdrawal led to a significant increase in morning BP and heart rate associated with an increase in urinary NE. To conclude, catecholamines seem to be robust biomarkers reflecting sympathetic overactivity, a key marker of OSA, make it possible to asses the impact of CPAP treatment on this intermediary mechanism.

Plasma biomarkers of metabolic syndrome in OSA

Background: metabolic syndrome and OSA

OSA is associated with all the components of the metabolic syndrome including visceral obesity [27], hypertension, poor glycemic control and lipid metabolism abnormalities. It has been suggested that adipocytes exposed to hypoxia exhibit dysregulated adipocytokine production [28], which may contribute to insulin resistance and metabolic syndrome in OSA patients. We have demonstrated in patients with morbid obesity that chronic intermittent hypoxia is strongly associated with higher systemic inflammation, nonalcoholic fatty liver disease (NAFLD) and with more severe fibrotic or inflammatory liver injuries [5,29]. A proposed mechanism would be the portal/fatty acids flux theory suggesting that visceral fat releases free fatty acids into the portal vein, which are delivered in high concentrations directly to the liver. This leads to accumulation of hepatic fat and the development of hepatic insulin resistance. Moreover, liver steatosis is not only responsible for liver mortality and morbidity but also contributes to extrahepatic manifestations including endothelial dysfunction [29] or atherosclerosis leading to cardiovascular diseases (CVD) [30]. Regarding lipid abnormalities, intermittent hypoxia leads to an increase in serum cholesterol and phospholipid levels, to an up-regulation of triglyceride and phospholipid biosynthesis, and to the inhibition of triglyceride uptake by the liver. Hypoxia is also associated with lipoprotein lipase inhibition in the adipose tissue resulting in an increase in plasma chylomicron and very low-density lipoprotein (VLDL)-cholesterol that may favor the progression of atherosclerosis [7].

Lipids

Summary of data from open studies

A higher prevalence of hyperlipidemia has been reported in patients with OSA. Oxygen desaturation, expressed using the oxygen desaturation index (ODI), is a significant independent factor contributing to hypercholesterolemia and hypertriglyceridemia [31]. However, recently, in 2081 OSA patients included in a prospective observational cohort, no association was found between total cholesterol or low-density lipoprotein (LDL)-cholesterol and the ODI. In contrast, the severity of the intermittent hypoxia was associated with higher triglyceride and lower high-density lipoprotein (HDL)-cholesterol levels, independently of the metabolic syndrome [32]. Open CPAP treatment studies showed a decrease in total cholesterol and apolipoprotein B in OSA patients demonstrating good CPAP compliance (>4 h/night) [33]. Moreover, a decrease in triglyceride levels has been observed after six months in CPAP patients with severe OSA [34]. Conversely, other open studies did not observe any effect of CPAP on triglyceride and cholesterol levels [35].

Data from RCTs: is CPAP treatment able to improve lipid metabolism?

The diagnosis of sleep apnea and the initiation of CPAP treatment are likely to induce changes in lifestyle and physical activity in some patients. As lipid and glucose metabolism are both very sensitive to changes in physical activity or diet it is essential that trials have a randomized sham-controlled design in order to address the question of the impact of CPAP on metabolic biomarkers.

In 2004, Robinson et al. [36] were the first to show a significant decrease in cholesterol (before vs after) of 0.28 mmol/L after one month of therapeutic CPAP treatment (Table 3). However, the difference between therapeutic CPAP and sham CPAP arms failed to attain significance. The duration of treatment was short and this suggested that this trend might become significant with longer exposure to CPAP. In 2007 two additional randomized trials [37,38] measured variations in cholesterol and triglycerides before and after CPAP/sham treatment and observed no change. These trials had the particularity of including morbidly obese OSA patients with limited CPAP adherence rates (mean therapeutic CPAP use less than 4 h/night). In the 2010 study by Lam et al. [22] no improvement in any lipid levels was seen after one week of therapeutic CPAP versus sham CPAP. Nevertheless, after a further 11 weeks with open CPAP the obese Asian patients (body mass index (BMI) $\geq$ 25 kg/m^2) showed some improvements in triglyceride, total cholesterol and apolipoprotein B levels but not those in the BMI < 25 kg/m^2) subgroup.

In RCTs single fasting measurements of lipid parameters did not catch any significant impact of CPAP. The only positive randomized sham-controlled trial [23] in this field built 24-h lipid concentration curves using seven blood samples drawn during both awake and sleeping periods. Therapeutic CPAP significantly reduced postprandial levels of triglycerides and total cholesterol.

In summary, although one study [23] confirmed that CPAP is able to reduce postprandial levels of lipids (that are recognized markers of cardiovascular risk), the impact of CPAP on lipid levels seems to be of limited clinical relevance compared to that of lipid lowering drugs. In the study by Robinson et al. [36], one month of CPAP induced a decrease of 0.28 mmol/L in cholesterol in the therapeutic CPAP arm, which was assigned as a 15% reduction in CVD risk by the authors. In comparison statins can lower LDL cholesterol concentration by an average of 1.8 mmol/L resulting in a reduction of about 60% in the risk of ischemic heart disease events [39]. A key issue in the metabolic response to CPAP is the impact of treatment on ectopic fat. Hoyos et al. [40] conducted a randomized sham-controlled study in sixty-five non-diabetic CPAP-naive men with moderate to severe OSA. Patients were randomized to receive either real ($n = 34$) or sham ($n = 31$) CPAP for 12 weeks. Main outcomes were the change from baseline to week 12 in insulin sensitivity, visceral abdominal fat and liver fat. They demonstrated that reduction in visceral abdominal fat and liver fat, both major components of metabolic syndrome, cannot be achieved with CPAP alone. Hoyos et al. [41] also retrospectively assayed stored blood from their RCT for lipids and extracted information regarding hypertension, hyperlipidemia and its treatment in order to diagnose metabolic syndrome. They found that CPAP therapy had no effect on

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Table 4
Effects of CPAP on glucose metabolism biomarkers. AHI: apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; HbA1c: hemoglobin A1c; HOMA: homeostatic model assessment; IR: insulin resistance; ISI: insulin sensitivity index; ISx: insulin sensitivity measured by minimal model analysis; ODI: oxygen desaturation index; OGTT: oral glucose tolerance test.

Author	Biomarkers of glucose metabolism	Main results	Comments
Coughlin et al, 2007 [37]	Fasting glucose, insulin, HOMA index	No change in parameters of glucose control	No order or carry-over effect for any outcome variables Intention-to-treat analysis and per protocol analysis with exclusion of patients with compliance < 3.5 h/night
West et al, 2007 [38]	Fasting glucose, insulin, HOMA index, HbA1c, euglycemic clamp	No change in both groups	No correlation between CPAP use and the measures of glycemic control or IR
Lam et al, 2010 [22]	Glucose, insulin, HOMA, Kitt: constant representing the insulin sensitivity estimated by the short insulin tolerance test (SITT)	**After 1 week:** **Increase in Kitt with CPAP only in obese (BMI > 25 kg/m², Asian patients with above this value are considered as obese)** No change for insulin, glucose, HOMA	**Sustained effect at 12 weeks**
Hoyos et al, 2012 [40]	Fasting glucose, insulin, HOMA, ISx	No changes at 12 weeks	CPAP compliance did not influence the effect on ISx
Sivam et al, 2012 [42]	Fasting glucose	No difference	
Weinstock et al, 2012 [54]	2-h OGTT, fasting glucose, fasting insulin, HbA1c, ISI, HOMA-IR, HOMA-B	**In those subjects with baseline AHI ≥ 30/h (n = 25), there was a 13.3% improvement in ISI and a 28.7% reduction in the 2-h insulin level after CPAP compared to sham CPAP**	7 subjects normalized their mean 2-h OGTT after CPAP but not after sham CPAP, while 5 subjects normalized after sham CPAP but not after CPAP. Overall, there was no improvement in ISI between CPAP and sham CPAP
Prudon et al, 2013 [52]	Euglycemic clamp, HOMA, HbA1c	No difference	
Kritikou et al, 2014 [53]	HOMA	No difference	Men: IR at baseline greater in OSA than in control group Stronger association between OSA and IR in men than in women
Kohler et al, 2011 [9]	Glucose, insulin, HOMA	No changes in CPAP withdrawal group compared to therapeutic CPAP group	At 2 weeks: CPAP withdrawal associated with significant: - increase in AHI, ODI, and number of arousals - decrease in endothelial function

the development or regression of metabolic syndrome [41]. Another study using magnetic resonance imaging to assess visceral and liver fat also failed to demonstrate any improvement [42]. In addition, in patients with minimally symptomatic OSA, a RCT comparing standard care to auto-adjusted CPAP showed that therapeutic CPAP does not appear to improve a calculated vascular risk that included a cholesterol component [43]. Finally, the CPAP withdrawal model used by Kohler et al. [9] demonstrated an increase in urinary catecholamines but did not lead to an increase in markers of systemic inflammation, insulin resistance, or blood lipids[1].

Glucose

Summary of data from open studies

Rapidly accumulating data from both epidemiologic and clinical studies have suggested that OSA is independently associated with alterations in glucose metabolism as well as with an increased risk of developing T2DM. In the Sleep Heart Health Study [46], the relation between sleep-disordered breathing and metabolic abnormalities was investigated in a large cohort of patients. Nocturnal hypoxemia was associated with glucose intolerance independently of age, sex, BMI and waist circumference. OSA severity was also associated with the severity of insulin resistance after adjustment for obesity [6,46]. Indeed, recent reports have indicated that more than 50% of patients with T2DM have OSA. Multiple mechanistic pathways contribute to the deterioration in plasma glucose/insulin homeostasis in OSA, the first one being sympathetic overactivity, due to sleep fragmentation and intermittent hypoxia. Independently of autonomic nervous system activation, in animal models intermittent hypoxia contributes to decreased glucose utilization in oxidative muscle fibres [47]. Intermittent hypoxia also seems to be responsible for increased beta-cell proliferation and cell death, the latter being due to oxidative stress [48]. OSA is also commonly associated with obesity. Besides T2DM, obesity is associated with low grade systemic inflammation, increased macrophage accumulation in adipose tissue and nonalcoholic fatty liver disease. Adipocytes exposed to hypoxia exhibit a dysregulated production of adipocytokines, which may contribute to alterations in glucose control in OSA patients.

In open studies, CPAP has been suggested as improving glucose metabolism in both diabetic and non-diabetic OSA patients [33,49]. However, a meta-analysis by Yang et al. [50] that included 15 mostly observational studies showed an improvement in homeostatic model assessment insulin resistance (HOMA-IR), whereas no change in fasting glucose was observed in non diabetic and diabetic subjects after CPAP treatment.

Data from RCTs: is CPAP treatment able to improve glucose metabolism and glycemic control?

We found nine randomized sham-controlled studies investigating the effect of CPAP on one or more glucose biomarkers (Table 4). As for lipids, a randomized design is crucial because glucose biomarkers are also very sensitive to patients' behaviors (physical exercise, diet, smoking), which may be modified when patients become aware of their sleep apnea diagnosis and are included in a clinical study. A major issue in the field of glucose control is that a wide range of measurements are used as outcomes. The index mostly used to measure IR in these studies was the

[1] Sharma et al. [44] have reported decreases in visceral fat, triglycerides and cholesterol after three months of CPAP treatment, but this article has been withdrawn from publication [45].

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

HOMA-IR, an index derived from fasting plasma glucose and fasting serum insulin. The gold standard for assessing IR is the euglycemic hyperinsulinic clamp; however, its availability is limited and the technique is difficult to implement in large RCT. In addition, several indices have been built from the results for plasma glucose and serum insulin during an oral glucose tolerance test that allows insulin sensitivity to be estimated from a dynamic and physiological oral glucose load [51]. Another limitation was that some studies addressed only diabetic patients while others included patients without diabetes or patients with impaired glucose control.

Data from randomized sham-controlled studies dealing with the effect of CPAP on glucose metabolism clearly appear less optimistic than open studies regarding the impact of CPAP on glucose control. Five out of the nine trials did not succeed in showing any improvement on glucose biomarkers [37,38,42,52,53]. Moreover, the two studies using the euglycemic clamp did not report any effect of CPAP [38,52]. On the contrary, in 2010 Lam et al. [22] were the first to report a positive effect of CPAP on IR in a randomized sham-controlled study, after one week of treatment. CPAP had a positive effect only in moderately obese patients (BMI > 25 kg/m^2). This beneficial effect on insulin sensitivity was maintained after the 12 weeks of open study CPAP in these patients. In a post-hoc analysis limited to severe OSA, Weinstock et al. [54] showed that the 2-h oral glucose tolerance test measuring glucose and insulin 2 h after the ingestion of 75 g of anhydrase glucose was improved as well as the insulin sensitivity index in the most severe OSA patients. In addition, Kohler et al. [9] showed no changes in glucose, insulin and thus in HOMA after two weeks of CPAP withdrawal.

The conflicting results concerning the impact of CPAP on glucose biomarkers have been addressed by two meta-analyses. The first one [55] included five randomized and one non-randomized studies. Overall it concluded that CPAP did not influence plasma insulin, HOMA-index or HbA1c. On the contrary, another meta-analysis [56] found that CPAP treatment in non diabetic OSA patients improved IR as assessed by HOMA-IR. The main limitation to this meta-analysis is the inclusion of the positive study by Sharma et al. henceforth withdrawn from publication [45]. This retracted study explained a major part of the positive result of the meta-analysis. Finally, Comondore et al. [57] did not use sham CPAP as placebo, since patients were randomized to CPAP or no therapy for four weeks in a cross-over design.

To conclude, the impact of CPAP on glucose biomarkers is uncertain and if existent is restricted and far from that of anti-diabetic agents. Further research is needed to establish whether CPAP combined with other glucose control medication is useful in patients with OSA and impaired glucose tolerance or diabetes. Also lifestyle intervention, particularly weight loss, not only reduces sleep apnea but also clearly improves diabetes control[2] [58].

Oxidative stress, and biomarkers of endothelial function

Background: oxidative stress, endothelial apoptosis and repair capacity in OSA

Intermittent hypoxia induces the generation of oxygen free radicals at the systemic and tissular levels. Oxidative stress plays a key role in activating intermediate mechanisms including sympathetic activation and vascular inflammation which in turn favor the development of OSA-related comorbidities such as hypertension, dyslipidemia and T2DM/IR. The potential synergistic effects of oxidative stress generated by IH itself and comorbidities enhance the overall burden of oxidative stress and the resultant inflammatory/immune cell activation. The enhanced oxidative stress exacerbates inflammation, generating a vicious cycle leading to cardiovascular morbidity [2] (Fig. 1). Oxidative stress partially explains vascular endothelium damage and therefore the increased risk of cardiovascular diseases in OSA [3]. Pancreatic β cells are very sensitive to oxidative stress which is involved in pancreatic cell death induced by IH in rodent models [48]. This underlying mechanism also contributes to NAFLD [59,60] and its progression to advanced stages of nonalcoholic steatohepatitis (NASH) and hepatic fibrosis that increase the risk of T2DM and cardiovascular diseases.

The inhibition of endothelial nitric oxide synthase (eNOS) accounts for a reduction in nitric oxide (NO) production reflected by a decrease in total nitrate and nitrite (NOx) [61]. The increase of endothelial apoptosis reduces eNOS activity leading to reduced NO production. Furthermore, oxidative stress can be modulated by microparticles derived from vascular and blood cells. Microparticles increase the expression of cyclooxygenase (Cox)-1 and Cox-2, and the production of thromboxane A2 and prostacyclin. All these mechanisms implicate microparticles in endothelial dysfunction, vascular inflammation and vascular hyperreactivity [62]. Vascular endothelium damage is caused not only by increased endothelial apoptosis, but is also linked to decreased repair capacities. Circulating progenitor cells (CPCs) are the markers of the endothelial repair capacity and their depletion also contributes to endothelial dysfunction. The CPC count is correlated with the Framingham risk score [63] and can predict future CVD events [64].

Summary of data from open studies

There are hundreds of OSA studies that include various markers of oxidative stress [65]. These open studies concur that oxidative stress is elevated and related to OSA severity [66]. The question remains as to the respective roles of OSA *per se* and comorbidities in the extent of increase in oxidative stress. Otherwise healthy OSA patients, without any comorbidities, do not manifest evidence for higher oxidative stress and lipid peroxidation when compared to carefully matched controls [67,68].

The effect of CPAP on oxidative stress biomarkers is also unclear; the majority of open studies showing a significant decrease in oxidative stress [17,66] and an increase in antioxidant capacity [69]. However, a single night of CPAP had no effect on antioxidant enzyme levels [70].

Concerning microparticles, open studies including a small number of patients showed a decrease in platelet-derived microparticles (PMPs) with CPAP [71,72].

Finally, the decrease in CPCs associated with OSA is also debated; three open studies [12,73,74] confirmed this reduction, whereas no change [75,76] or only a downward trend [77] was reported in three other open studies. The effect of CPAP on CPCs was investigated in five studies providing divergent results [12,73–76], but the CPAP intervention was not randomized. While some studies showed a short term increase in CPCs (CD34+/KDR+/CD133+ [12] and CD34+/KDR+/CD133+/CD45− [74]) with CPAP, larger studies with a longer treatment duration [75,76] did not confirm these findings.

Data from RCTs: is CPAP treatment able to reduce oxidative stress and to improve biomarkers of endothelial function?

Surprisingly, the impact of CPAP on oxidative stress, which is the central intermediate mechanism of OSA, has only been investigated in one randomized sham-controlled trial [19] (Table 5). This trial included 31 OSA men in a cross-over design and showed improvement in oxidative stress and increase in nitrates after 12 weeks of therapeutic CPAP treatment compared to sham CPAP. CPAP significantly decreased 8-isoprostanes and increased total

[2] Sharma et al. [44] reported no change in glucose, insulin and HOMA index whereas decreases in HbA1c and in the frequency of metabolic syndrome were observed.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Table 5
Effects of CPAP on oxidative stress and endothelial function biomarkers. AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; CPCs: circulating progenitor cells; EMPs: endothelium-derived microparticles; ESS: Epworth sleepiness scale; GMPs: granulocyte-derived microparticles; KDR: kinase insert domain receptor; LMPs: leukocyte-derived microparticles; MPs: microparticles; NOx: total nitrite and nitrate; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PAT: peripheral arterial tone; PMPs: platelet-derived microparticles; RHI: reactive hyperemia index.

Author	Biomarkers of oxidative stress and endothelial function	Main results	Comments
Alonso Fernandez et al, 2009 [19]	8-isoprostanes NOx	**Decrease in 8-isoprostanes and increase in NOx**	At baseline: Plasma levels of 8-isoprostanes were higher in OSA compared to controls and NOx levels were lower No correlation between 8-isoprostanes or NOx and OSA severity Values after CPAP not different from those found in control subjects Data presented in per protocol analysis: 2 patients excluded for average night CPAP usage < 3.5h No intention-to-treat analysis reported.
Ayers et al, 2013 [10]	Circulating cell-derived MPs : PMPs, LMPs and EMPs.	**Increase in EMPs (CD62E+, CD106+), GMPs (CD66B+) after CPAP withdrawal but only CD62E+ change was significant** No change in CD31+ CD41− EMPs and PMPs or CD45+ LMPs	At baseline, CD62E+ EMPs levels were higher in therapeutic CPAP group but difference between groups held true, even after correction for the baseline levels As expected, withdrawal of CPAP increased AHI, ODI and ESS score
Simpson et al, 2013 [78]	CPCs levels by 2 methods: - flow cytometry - co-staining culture with acLDL and lectin	No change in all CPCs levels (CD34+/KDR+, CD34+/KDR+/CD45+, acLDL+/lectin+)	At baseline, CD34+/KDR+/CD45− levels lower in CPAP group No correlation between OSA severity and CPCs levels or RHI Correlation between RHI and cultured acLDL+/lectin+ CPCs but not with antigen-defined CPCs Intention-to-treat analysis CPAP did not improve PAT

NOx. Mean compliance was particularly high (6.2 h/night) and there was no intention-to-treat analysis reported: patients with CPAP use <3.5 h/night were excluded and results reported as per-protocol. Moreover, there was no wash-out period with a potential carry-over effect. Therefore it is difficult to firmly conclude from this single RCT and to generalize these results to the general OSA population.

There are few randomized sham-controlled trials investigating the effects of CPAP on CPCs and microparticles. Ayers et al. [10] showed significant increases in endothelium-derived microparticles (EMPs) CD62E+, CD106+ and granulocyte-derived microparticles (GMPs) CD66B+ after CPAP withdrawal. However, only EMPs CD62E+ were increased after two weeks of CPAP withdrawal compared with a continuous CPAP group, whereas no change in GMPs, leukocyte-derived microparticles (LMPs) and PMPs was observed. Potentially, the decrease in EMP levels might be an underlying mechanism in the improvement in endothelial function that occurs under CPAP.

Finally, the only randomized sham-controlled trial evaluating the effect of CPAP on CPCs [78] did not confirm the increase in CD34+/KDR+ and CD34+/KDR+/CD45− CPCs previously reported in open studies [12,74].

Inflammation

Background: inflammation and intermittent hypoxia

As stated above, low grade inflammation induced by oxidative stress and sympathetic overactivity will in turn lead to endothelial

Table 6
Effects of CPAP on inflammatory blood markers. AHI: apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; CRP: C-reactive protein; IFN: interferon; IL: interleukin; LT: leukotriene; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; SaO_2: oxygen saturation.

Author	Blood biomarkers of Inflammation	Main results	Comments
West et al, 2007 [38]	CRP, adiponectin	No significant changes	Lower baseline adiponectin in placebo CPAP group
Arias et al, 2008 [18]	IL-6, TNF-α, LTB4, TNFR-1	**Significant decrease in TNFR-1** No changes in IL-6, TNF-α, and LTB4.	At baseline: OSA > control for TNFR-1 levels, No significant difference in IL-6, LTB4 and TNF-α between OSA and control. Positive correlation between sTNFR-1, IL-6 levels and BMI in OSA patients but no significant relationships between sleep parameters (AHI, ODI, mean and minimum nocturnal SaO_2) and plasma cytokine levels
Kohler et al, 2009 [87]	IL-6, CRP, IFNγ, adiponectin	No significant changes	No significant correlation between any of the inflammatory markers and the ODI at baseline The lack of a change in adiponectin may be due to an overwhelming impact of obesity on adiponectin secretion as BMI was relatively high in the study population Short duration of treatment
Hoyos et al, 2012 [40]	Leptin, adiponectin	No significant changes	At baseline: correlation between BMI and leptin No correlation between BMI and adiponectin No change at 24 weeks
Prudon et al, 2013 [52]	Adiponectin	No significant changes	
Kritikou et al, 2014 [53]	IL-6, CRP, TNFR-1, leptin, adiponectin	No significant changes even after subgroup analysis (low and high adherence)	At baseline: Men: OSA > control for CRP, IL-6, and leptin Women: OSA > control only for CRP No difference in IL-6, TNFR-1, leptin and adiponectin between OSA and control women Stronger association between OSA and inflammation in men than in women at baseline
Kohler et al, 2011 [9]	CRP, IL-6, IL-8, TNF-α	No changes in systemic inflammation measures	At 2 weeks: CPAP withdrawal associated with significant: - increase in AHI, ODI, and number of arousals - decrease in endothelial function

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

dysfunction, early atherosclerosis, hypertension, that finally cause cardiometabolic morbidity and mortality (Fig. 1).

Obesity and T2DM frequently associated with OSA also contribute to low-grade systemic inflammation, increased macrophage accumulation in adipose tissue and NAFLD. Adipose tissue inflammation and local hypoxia at the fatty tissue level may play a role in OSA-associated morbidity by increasing release of cytokines, tumor necrosis factor (TNF)-α, pro-atherogenic chemokines, and pro-angiogenic peptides [6]. This dysregulation of adipocytokine production may contribute to insulin resistance and an increased risk of metabolic syndrome associated with OSA [37].

Summary of data from open studies

A large number of studies have assessed a wide panel of circulating inflammatory mediators, but mainly C-reactive protein (CRP) and interleukin (IL)-6. Collectively the data support the systemic inflammation associated with OSA [79]. Although some open studies suggest a decrease of inflammatory biomarkers after CPAP treatment [79], the true effect is still debated [80].

Three meta-analyses have tried to clarify the effect of CPAP on inflammatory biomarkers [81–83]. None of them restricted data to sham-controlled trials. The first one [82] investigated the effect of CPAP specifically on CRP. Fourteen case-control studies were included; eight reported a decrease in CRP after CPAP treatment whereas six did not show any beneficial effect. The second meta-analysis [81] included 24 studies mainly with a case-control design except for the trial of Arias et al. [18] (14 studies for CRP, nine for TNF-α and eight for IL-6). They report improvements in CRP and TNF-α and showed a trend towards decreased IL-6 levels after CPAP treatment. Similarly, Xie et al. [83] reported a decrease in CRP and TNF-α, in addition to that of IL-8, and confirmed the non-significant decrease in IL-6 reported by Baessler et al. [81]. Thirty five studies were included in this meta-analysis, 24 for CRP, 16 for IL-6, 12 for TNF-α and only three for IL-8.

Data from RCTs: is CPAP treatment able to reduce systemic inflammation?

We have reviewed six randomized sham-controlled trials exploring one or more inflammatory biomarkers (Table 6). None of these studies demonstrated a reduction in adiponectin, highly sensitive CRP, IL-6, leptin, interferon, TNF-α and leukotrienes B4. Furthermore, Kohler et al. [9] did not show an increase in inflammatory markers (CRP, IL-6, IL-8, TNF-α) after CPAP withdrawal.

The only inflammatory biomarker found to improve with CPAP is tumor necrosis factor receptor (TNFR)-1. Arias et al. [18] showed higher TNFR-1 levels in OSA patients than in controls, with levels significantly decreased after 12 weeks of CPAP in compliant patients. Kritikou et al. [53] did not confirm changes in TNFR-1 after two months of CPAP (CPAP compliance close to 6 h/night). The single positive RCT needs to be replicated but nevertheless opens interesting physiopathological perspectives. TNFR-1 seems to be a better marker for the biological response than TNF-α. TNFR-1 also seems to be an accurate prognostic factor in chronic diseases [84], closely linked to glucose metabolism and plays a key role in the pathogenesis of obesity [85]. Furthermore, TNFR-1 seems to be significantly correlated with sleep architecture and fragmentation [86].

In summary, the lack of any benefit of CPAP on inflammatory markers might be attributed to the short term duration of the studies [53,87], or to different levels of CPAP usage [38,40,52] but may more probably reflect the overwhelming impact of obesity and comorbidities on low grade inflammation, that is not reversed by CPAP.

Liver enzymes

Background: the liver and OSA

The prevalence of NAFLD is an increasing concern and becomes a major health problem and is associated with metabolic syndrome and cardiovascular diseases [30]. In addition to the classical risk factors for NAFLD such as obesity, hyperlipidemia and diabetes, OSA recently emerged as a new central contributor to NAFLD [5,88]. After adjustment for confounders, severe OSA is associated with an increased risk of elevated liver enzymes, and more severe stages of steatosis, fibrosis, and necrosis in liver biopsies [5,59,88]. Both OSA and NAFLD act synergistically towards the development of metabolic syndrome and cardiovascular diseases [30].

Summary of data from open studies

Several open studies suggest that CPAP may positively impact on liver biomarkers. Chin et al. [89] reported higher aspartate aminotransferase (AST) levels after sleep compared to the previous afternoon in OSA patients. A single night of CPAP treatment was sufficient to reduce AST levels with a sustained improvement after one to six months of CPAP treatment. In addition, 2–3 y of CPAP was found to partially reverse moderate to severe steatosis as assessed by a computed tomography scan, with concurrent improvement in liver enzyme levels [60].

Data from RCTs: is CPAP treatment able to decrease liver enzymes?

Only two randomized sham-controlled trials have investigated the effects of CPAP on liver biomarkers [42,90] (Table 7). In 2009, Kohler et al. [90] failed to show any correlation between aminotransferase levels and ODI at baseline. They investigated the impact of CPAP on liver enzymes (alanine aminotransferase (ALT) and AST) as primary outcome and showed that four weeks of CPAP treatment decreased ALT levels in both CPAP and sham CPAP groups, but the difference between arms was not significant. We note that 77% of patients had levels within the normal range at baseline. Sivam et al. [42] in a cross-over study including one month wash-out also showed that AST and ALT levels did not change despite longer CPAP exposure. No significant difference was found for γ-

Table 7
Effect of CPAP on liver enzymes. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CPAP: continuous positive airway pressure; GGT: γ-glutamyltransferase; ODI: oxygen desaturation index; OSA: obstructive sleep apnea.

Author	Liver biomarkers	Main results	Comments
Kohler et al, 2009 [90]	ALT AST	ALT decrease in both CPAP and sham CPAP group but no difference between arms No change in AST	At baseline: 77% of OSA patients had liver enzyme levels within normal range No correlation between AST or ALT and BMI No correlation between AST or ALT and ODI Intention-to-treat and per protocol analysis
Sivam et al, 2012 [42]	ALT AST ALP GGT Albumin Bilirubin Total protein	No change in ALT, AST, GGT, albumin, bilirubin and total protein **Decrease in ALP**	At baseline, mean values were within the normal range but half of the patients had mildly elevated liver enzyme levels

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

glutamyltransferase, bilirubin, total albumin and total protein reflecting no biochemical effect on the synthesis and detoxification function of the liver. In contrast, alkaline phosphatase (ALP) levels decreased significantly, but the significance of an isolated reduction in ALP is unclear. Again in this study, liver enzymes at baseline were either normal or only mildly elevated.

It should be noted that, liver enzymes are not specific markers of NAFLD and are not modified in 50–80% of NAFLD patients [91]. Non-invasive blood tests (SteatoTest®, NASHTest® and FibroTest®) are available for evaluating steatosis, NASH and fibrosis [92]. In a large unselected OSA population, the severity of nocturnal hypoxia was independently associated with steatosis assessed by SteatoTest® [29]. These non-invasive blood tests are more specific of NAFLD and their evolution after CPAP treatment certainly needs to be investigated.

The effect of CPAP on liver fat has also been assessed by imaging techniques in randomized sham-controlled studies. In line with the absence of any effect on liver enzymes, Hoyos et al. [40] showed no difference in liver fat after 12 or 24 weeks of CPAP treatment. Likewise, Lam et al. [22] confirmed the lack of effect of CPAP on intra-abdominal fat after 12 weeks of treatment.

Blood coagulation markers

Background: hemostatic imbalance and intermittent hypoxia

A number of observational studies have suggested that OSA is associated with increased coagulability and decreased fibrinolytic capacity. Hemostatic imbalance between the coagulation and fibrinolysis systems results in a prothrombotic state contributing to a high risk of thrombosis in OSA patients [93]. In OSA patients, platelets exhibit increased *in vitro* activation and aggregability. Mainly in severe OSA, P-selectin (CD62P) expression is increased. In addition, increased haematocrit, blood viscosity and fibrinogen levels seem to affect hypercoagulability and potentially contribute to CVD morbidity [2]. Coagulation markers display a circadian rhythm with a cycle that shows increased coagulability in the early morning. This temporal pattern coincides with a peak in the occurrence of cardiovascular events. Recently, a difference between OSA and non OSA patients in the day/night rhythm of coagulation biomarkers has been suspected [94].

Summary of data from open studies

Some improvements following CPAP treatment have been observed, including a reduction in platelet activation [95] and a decrease in plasminogen activator inhibitor-1 [96]. However, results are conflicting and some coagulation biomarkers such as von Willebrand factor (vWF), D-dimer or soluble tissue factor [96] have been reported as being unchanged after CPAP treatment.

Data from RCTs: is CPAP treatment able to improve coagulation biomarkers?

In 2004, Robinson et al. [36] showed that baseline levels of activated factor XIIa, VIIa, thrombin-antithrombin and soluble P-selectin in OSA patients were elevated compared to unmatched controls. These coagulation abnormalities are biologically significant; indeed factor XIIa is an initiator of fibrinolysis and FVIIa plays a central role in clot formation and is important in inducing the thrombogenic potential of atherosclerotic plaque as it is a cell surface molecule involved in leukocytes rolling and attachment. However, there was no significant decrease in these factors after one month of therapeutic CPAP versus sham CPAP (Table 8).

Three randomized sham-controlled studies [94,97,98] have investigated day/night fluctuations in several coagulation biomarkers and the effects of CPAP on these variations. In the study of Von Känel [94], OSA patients showed lower mesor (mean) and amplitude (difference between maximum and minimum activity) of D-dimer compared with controls. Therapeutic CPAP treatment for three weeks did not affect day/night rhythms of prothrombotic markers in OSA patients any differently from sham CPAP. In the randomized crossover trial of Phillips et al. [98], 28 patients received therapeutic or sham CPAP, each for two months with a one month washout between treatments. After each treatment period, a 24 h coagulation study was conducted for several coagulation markers.

Table 8
Effects of CPAP on coagulation factors. CPAP: continuous positive airway pressure; MAP: mean arterial pressure; OCP: overall coagulation potential; OFP: overall fibrinolysis potential; OHP: overall haemostasis potential; OSA: obstructive sleep apnea; PAI-1: plasminogen activator inhibitor; SaO_2: oxygen saturation; sP-selectin: soluble P-selectin; sTF: soluble tissue factor; TAT: thrombin-antithrombin; TIB: time in bed; tPA: tissue plasminogen activator; vWFAg: von Willebrand factor antigen.

Author	Biomarkers of coagulation	Main results	Comments
Robinson et al, 2004 [36]	Fibrinogen, VII, VIII, XII, TAT, XIIa (n = 46) VIIa (n = 44) homocystein (n = 101) vWFAg (n = 90) sP selectin (n = 93)	No changes in CPAP group FVIIa and FXII levels significantly decreased only in sham CPAP group No difference between arms	At baseline: fibrinogen, FVII, VIII, XII, vWFAg and homocysteine: within normal ranges XIIa, VIIa, TAT and sP-selectin: OSA > unmatched control No correlations between baseline raised VIIa, XIIa and TAT, with BMI, age and severity of OSA
McEwen et al, 2012 [97]	Fibrin generation: OHP: overall haemostasis potential (presence of tPA) OCP: overall coagulation potential (absence of tPA) Fibrinolysis: OFP: overall fibrinolysis potential OFP (%) = [(OCP-OHP)/OCP)] x 100	No difference on fibrin generation (OHP, OCP) and fibrinolysis (OFP) No alteration of the diurnal night-time profile	Positive correlations between OHP and fibrinogen and FVIII PAI-1 negatively correlated with OFP Increase in OHP and OCP at 9:00 am compared to 3:00 PM the previous day and night-time Decrease in OFP at 9:00 am compared to 3:00 pm the previous day and at midnight
Phillips et al, 2012 [98]	PAI1, D dimer, fibrinogen, vWF, FVIII, FVII, FV 24h	**CPAP reduced the early morning level of vWF, and nocturnal levels of FVIII and FV** No changes in fibrinogen, D-dimer, FVII and PAI-1 for the CPAP group	All coagulation markers displayed discrete diurnal variations
Von Kanel et al, 2013 [94]	PAI-1, D-dimer, vWFAg, sTF	No significant change under therapeutic CPAP	AHI: CPAP > sham CPAP Adjusted for age, BMI, and MAP: shape of the day/night pattern in D-dimer and PAI-1 did not vary between OSA and controls sTF and VWF did not show a significant day/night pattern Day/night pattern in D-dimer differed between OSA and controls Significant associations between BMI and PAI-1 and between MAP and PAI-1 Adjusted for age, BMI, MAP and SaO2 <90% of TIB: D-dimer mesor and amplitude: OSA < controls PAI-1 mesor did not differ significantly between OSA and controls whereas in unadjusted model PAI-1 mesor: OSA > controls

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

CPAP reduced the early morning level of vWF, and nocturnal levels of factor VIII and factor V. These findings suggest that CPAP may reduce cardiovascular risk in OSA, in part by reducing the risk of thrombosis. In the study by McEwen et al. [97], there was no difference in fibrin generation between CPAP and sham CPAP.

Discussion-perspectives

As OSA is clearly associated with metabolic and cardiovascular diseases, reducing cardiometabolic risk may represent an important target for effective OSA treatment. However, the impact of CPAP, the first line therapy of OSA, on cardiovascular or metabolic consequences is still debated.

Intermittent hypoxia the landmark of obstructive sleep apnea, induces oxidative stress and consequently promotes sympathetic activation, inflammation and endothelial dysfunction leading to cardiometabolic comorbidities. By considering the intermediary mechanisms involved in OSA pathophysiology, this review addressed the impact of CPAP on: 1) plasma and urine catecholamines and their metabolites reflecting sympathetic activity; 2) biomarkers of insulin resistance and lipid metabolism; 3) biomarkers of oxidative stress; and systemic and vascular inflammation; 4) liver enzymes; 5) biomarkers of coagulation. Hundreds of open studies have assessed the impact of CPAP on these biomarkers and in general reported a positive effect. However, many of these studies from patients attending sleep clinics are often flawed by selection bias based on the recruitment sources and poor adjustment for confounders. The majority of studies recruited small numbers of patients with periods on CPAP of short duration. Aiming to identify reliable information in the field, we restricted our review to randomized trials comparing therapeutic CPAP versus sham CPAP as a comparator.

These well controlled studies firmly established that CPAP has a beneficial effect mainly on sympathetic activity. The impact of CPAP on sympathetic activity is robust across studies and occurs rapidly. The significant reduction of sympathetic overactivity is probably one of the main mechanisms explaining the blood pressure reduction occurring in CPAP treated OSA patients. Meta-analyses have demonstrated that CPAP reduces 24-h mean BP by approximately 2 mmHg (pooled estimated effect). The blood pressure reduction associated with CPAP treatment occurs only in CPAP compliers with the highest BP levels at baseline i.e., subgroups showing the largest reduction in sympathetic activity with CPAP.

In contrast to sympathetic activity, the well-designed studies included in this review failed to demonstrate that CPAP alters metabolic or inflammatory markers in OSA. CPAP did not change glucose, lipids, IR levels or the ratio of patients with metabolic syndrome. However, it is difficult to formally conclude to the failure of CPAP therapy to improve metabolic disorders in OSA. Rather, we should consider this an opportunity to perform better-designed trials with larger sample sizes and longer treatment durations. Treatment compliance is also a key parameter and has been correlated to metabolic changes [99].

In obese OSA, the insulin sensitivity is likely to be determined primarily by obesity and, to a lesser extent, by sleep apnea. Accordingly, a recent meta-analysis did not show a significant impact of CPAP treatment on glucose homeostasis. The single positive study regarding lipids using seven blood samples drawn across both awake and sleeping periods only showed that CPAP improved postprandial triglycerides and mean 24-h total cholesterol levels. This is in accordance with the lack of effect demonstrated by CPAP on visceral fat. The Hoyos's study [40] suggests that reduction in visceral abdominal fat and liver fat, central components of metabolic syndrome cannot be achieved with CPAP alone. Another study from the same group using magnetic resonance imaging for assessing visceral and liver fat also failed to demonstrate any reduction in ectopic fat.

Are there some sub-groups of OSA patients that respond to CPAP better than others? An explanation for the heterogeneity in CPAP response is related to the severity of the disease. A recent RCT did not show that impaired glucose tolerance normalized after CPAP. However, insulin sensitivity improved in those with apnea–hypopnea index (AHI) $\geq$ 30/h, suggesting beneficial metabolic effects of CPAP only in patients with severe sleep apnea. A major issue is also the optimal duration for CPAP use. There is little data to establish a clear threshold of CPAP use that provides a reduction in cardiometabolic risks. It has been suggested from a meta-analysis that there is a dose–response relationship between the obtained reduction in blood pressure and nightly usage of the CPAP device. Hoyos et al. showed that there was no relationship between CPAP adherence and change in visceral abdominal fat and no effect was found even in high CPAP compliers.

In summary, it is not realistic to expect a clinically relevant decrease in cardiometabolic biomarkers with CPAP therapy. In unselected OSA patients, there is only a fringe benefit of CPAP on metabolic dysfunction.

Potentially, only certain target populations, such as severe patients without morbid obesity and on condition of high CPAP usage, would respond. Moreover, the range of response is not equivalent to that of lipid lowering drugs or weight loss programs.

Whereas the majority of respiratory physicians limit their intervention to prescribing CPAP, there is a need to offer multiple modalities of treatment to OSA patients if their cardiovascular and metabolic risk profile is to be successfully modified. Rehabilitation programs as well as weight loss reduction programs should probably be more frequently implemented in the field of OSA. Recently, Chironos et al. [100] compared the effect of combined interventions (CPAP and weight loss) to CPAP or weight loss alone. They showed that CPAP did not decrease any cardiometabolic biomarker, whereas combined interventions and weight loss alone induced significant decreases in CRP, insulin resistance and triglycerides. This recent study directly raises the question of the feasibility and ethics of the use of sham CPAP as a control arm over several months. A new strategy for clinical trials in this field would be to implement designs that allow different combinations of therapies, with or without CPAP to be assessed. Clinicians should adapt treatment modalities to the different phenotypes and clusters of comorbidities. This might allow the design and validation of innovative and personalized therapeutic strategies targeting predefined phenotypes of interest. Further research is also needed to establish what the best strategy is when combining CPAP with other lipid-lowering medication(s), antiinflammatory and/or antioxidant drugs in order to improve cardio-metabolic parameters.

Practice points

- The association of OSA and comorbidities may magnify the cardiovascular risk factors, aggravating mortality.
- Reducing cardiometabolic risk may represent an important target for effective OSA treatment.
- CPAP is unlikely to have a major effect on metabolic health in unselected individuals with OSA.
- The existence of OSA-related comorbidities implies the need to develop tailored combined therapeutic modalities with a follow-up adapted to patients' complexity.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

Research agenda

- To conduct randomized controlled trials combining CPAP with other interventions such as physical activity and weight loss programs.
- To establish what the best strategy is to combine CPAP with other lipid-lowering medication, antiinflammatory and antioxidant drugs to improve cardio-metabolic parameters.
- Additional mechanistic studies should also explore why ectopic fat does not respond to CPAP intervention. This should be done primarily in animal models exposed to intermittent hypoxia.

Acknowledgment

We thank Dr Alison Foote (Clinical Research Center, Grenoble University Hospital) for language editing.

References

[1] Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677–85.
*[2] Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. Eur Respir J 2009;33:1467–84.
*[3] Levy P, Tamisier R, Minville C, Launois S, Pepin JL. Sleep apnoea syndrome in 2011: current concepts and future directions. Eur Respir Rev 2011;20:134–46.
[4] McNicholas WT, Bonsigore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007;29:156–78.
[5] Aron-Wisnewsky J, Minville C, Tordjman J, Levy P, Bouillot JL, Basdevant A, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. J Hepatol 2012;56:225–33.
[6] Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. Eur Respir J 2009;34:243–60.
*[7] Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol 2013;62:569–76.
*[8] Pepin JL, Tamisier R, Levy P. Obstructive sleep apnoea and metabolic syndrome: put CPAP efficacy in a more realistic perspective. Thorax 2012;67:1025–7.
*[9] Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, Russi EW, et al. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2011;184:1192–9.
[10] Ayers L, Stoewhas AC, Ferry B, Stradling J, Kohler M. Elevated levels of endothelial cell-derived microparticles following short-term withdrawal of continuous positive airway pressure in patients with obstructive sleep apnea: data from a randomized controlled trial. Respiration 2013;85:478–85.
*[11] Lavie L. Obstructive sleep apnoea syndrome–an oxidative stress disorder. Sleep Med Rev 2003;7:35–51.
*[12] Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 2008;117:2270–8.
[13] Tamisier R, Pepin JL, Remy J, Baguet JP, Taylor JA, Weiss JW, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J 2011;37:119–28.
[14] Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90:47–112.
[15] Hedner J, Darpo B, Ejnell H, Carlson J, Caidahl K. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications. Eur Respir J 1995;8:222–9.
[16] Heitmann J, Ehlenz K, Penzel T, Becker HF, Grote L, Voigt KH, et al. Sympathetic activity is reduced by nCPAP in hypertensive obstructive sleep apnoea patients. Eur Respir J 2004;23:255–62.
[17] Pinto P, Barbara C, Montserrat JM, Patarrao RS, Guarino MP, Carmo MM, et al. Effects of CPAP on nitrate and norepinephrine levels in severe and mild-moderate sleep apnea. BMC Pulm Med 2013;13:13.
[18] Arias MA, Garcia-Rio F, Alonso-Fernandez A, Hernanz A, Hidalgo R, Martinez-Mateo V, et al. CPAP decreases plasma levels of soluble tumour necrosis factor-alpha receptor 1 in obstructive sleep apnoea. Eur Respir J 2008;32:1009–15.
[19] Alonso-Fernandez A, Garcia-Rio F, Arias MA, Hernanz A, de la Pena M, Pierola J, et al. Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial. Thorax 2009;64:581–6.
[20] Ziegler MG, Mills PJ, Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. Chest 2001;120:887–93.
[21] Grote L, Kraiczi H, Hedner J. Reduced alpha- and beta(2)-adrenergic vascular response in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2000;162:1480–7.
[22] Lam JC, Lam B, Yao TJ, Lai AY, Ooi CG, Tam S, et al. A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. Eur Respir J 2010;35:138–45.
[23] Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. Am J Respir Crit Care Med 2011;184:355–61.
[24] Kohler M, Pepperell JC, Casadei B, Craig S, Crosthwaite N, Stradling JR, et al. CPAP and measures of cardiovascular risk in males with OSAS. Eur Respir J 2008;32:1488–96.
[25] Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. J Appl Physiol (1985) 2006;100:343–8.
[26] Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J 2006;27:1106–13.
[27] Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151–8.
[28] Testelmans D, Tamisier R, Barone-Rochette G, Baguet JP, Roux-Lombard P, Pepin JL, et al. Profile of circulating cytokines: impact of OSA, obesity and acute cardiovascular events. Cytokine 2013;62:210–6.
*[29] Minville C, Hilleret MN, Tamisier R, Aron-Wisnewsky J, Clement K, Trocme C, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. Chest 2014;145:525–33.
[30] Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. Hepatology 2014;59:1174–97.
[31] Chou YT, Chuang LP, Li HY, Fu JY, Lin SW, Yang CT, et al. Hyperlipidaemia in patients with sleep-related breathing disorders: prevalence & risk factors. Indian J Med Res 2010;131:121–5.
*[32] Trzepizur W, Le Vaillant M, Meslier N, Pigeanne T, Masson P, Humeau MP, et al. Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. Chest 2013;143:1584–9.
[33] Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. Chest 2008;134:686–92.
[34] Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. Chest 2000;118:580–6.
[35] Michailidis V, Steiropoulos P, Nena E, Papanas N, Maltezos E, Bouros D. Continuous positive airway pressure treatment: effect on serum lipids in patients with obstructive sleep apnoea. Open Cardiovasc Med J 2011;5:231–8.
[36] Robinson GV, Pepperell JC, Segal HC, Davies RJ, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. Thorax 2004;59:777–82.
[37] Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM. Cardiovascular and metabolic effects of CPAP in obese males with OSA. Eur Respir J 2007;29:720–7.
[38] West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax 2007;62:969–74.
[39] Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423.
[40] Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. Thorax 2012;67:1081–9.
[41] Hoyos CM, Sullivan DR, Liu PY. Effect of CPAP on the metabolic syndrome: a randomised sham-controlled study. Thorax 2013;68:588–9.
[42] Sivam S, Phillips CL, Trenell MI, Yee BJ, Liu PY, Wong KK, et al. Effects of 8 weeks of continuous positive airway pressure on abdominal adiposity in obstructive sleep apnoea. Eur Respir J 2012;40:913–8.
*[43] Craig SE, Kohler M, Nicoll D, Bratton DJ, Nunn A, Davies R, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax 2012;67:1090–6.

* The most important references are denoted by an asterisk.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

[44] Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med 2011;365:2277–86.
[45] Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, et al. Retraction: CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med 2011;365:2277–86. N Engl J Med. 2013;369:1770.
[46] Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004;160:521–30.
[47] Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, et al. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 2007;175:851–7.
[48] Xu J, Long YS, Gozal D, Epstein PN. Beta-cell death and proliferation after intermittent hypoxia: role of oxidative stress. Free Radic Biol Med 2009;46:783–90.
[49] Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med 2005;165:447–52.
[50] Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath 2013;17:33–8.
[51] Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. Diabetes Care 2007;30:89–94.
[52] Prudon B, Roddy E, Stradling JR, West SD. Serum urate levels are unchanged with continuous positive airway pressure therapy for obstructive sleep apnea: a randomized controlled trial. Sleep Med 2013;14:1419–21.
[53] Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, Tsaoussoglou M, et al. Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females. Eur Respir J 2014;43:145–55.
[54] Weinstock TG, Wang X, Rueschman M, Ismail-Beigi F, Aylor J, Babineau DC, et al. A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. Sleep 2012;35:617–625B.
[55] Hecht L, Mohler R, Meyer G. Effects of CPAP-respiration on markers of glucose metabolism in patients with obstructive sleep apnoea syndrome: a systematic review and meta-analysis. Ger Med Sci 2011;9. Doc20.
[56] Iftikhar IH, Khan MF, Das A, Magalang UJ. Meta-analysis: continuous positive airway pressure improves insulin resistance in patients with sleep apnea without diabetes. Ann Am Thorac Soc 2013;10:115–20.
[57] Comondore VR, Cheema R, Fox J, Butt A, John Mancini GB, Fleetham JA, et al. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. Lung 2009;187:17–22.
[58] Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med 2009;169:1619–26.
[59] Norman D, Bardwell WA, Arosemena F, Nelesen R, Mills PJ, Loredo JS, et al. Serum aminotransferase levels are associated with markers of hypoxia in patients with obstructive sleep apnea. Sleep 2008;31:121–6.
[60] Shpirer I, Copel L, Broide E, Elizur A. Continuous positive airway pressure improves sleep apnea associated fatty liver. Lung 2010;188:301–7.
[61] Weiss JW, Liu Y, Li X, Ji ES. Nitric oxide and obstructive sleep apnea. Respir Physiol Neurobiol 2012;184:192–6.
[62] Trzepizur W, Martinez MC, Priou P, Andriantsitohaina R, Gagnadoux F. Microparticles and vascular dysfunction in obstructive sleep apnoea. Eur Respir J 2014;44:207–16.
[63] Hill JM, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003;348:593–600.
[64] Schmidt-Lucke C, Rossig L, Fichtlscherer S, Vasa M, Britten M, Kamper U, et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. Circulation 2005;111:2981–7.
[65] Volna J, Kemlink D, Kalousova M, Vavrova J, Majerova V, Mestek O, et al. Biochemical oxidative stress-related markers in patients with obstructive sleep apnea. Med Sci Monit 2011;17:CR491–7.
[66] Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest 2003;124:1386–92.
[67] Ozturk L, Mansour B, Yuksel M, Yalcin AS, Celikoglu F, Gokhan N. Lipid peroxidation and osmotic fragility of red blood cells in sleep-apnea patients. Clin Chim Acta 2003;332:83–8.
[68] Svatikova A, Wolk R, Lerman LO, Juncos LA, Greene EL, McConnell JP, et al. Oxidative stress in obstructive sleep apnoea. Eur Heart J 2005;26:2435–9.
[69] Barcelo A, Barbe F, de la Pena M, Vila M, Perez G, Pierola J, et al. Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. Eur Respir J 2006;27:756–60.
[70] Wali SO, Bahammam AS, Massaeli H, Pierce GN, Iliskovic N, Singal PK, et al. Susceptibility of LDL to oxidative stress in obstructive sleep apnea. Sleep 1998;21:290–6.
[71] Geiser T, Buck F, Meyer BJ, Bassetti C, Haeberli A, Gugger M. In vivo platelet activation is increased during sleep in patients with obstructive sleep apnea syndrome. Respiration 2002;69:229–34.
[72] Maruyama K, Morishita E, Sekiya A, Omote M, Kadono T, Asakura H, et al. Plasma levels of platelet-derived microparticles in patients with obstructive sleep apnea syndrome. J Atheroscler Thromb 2012;19:98–104.
[73] de la Pena M, Barcelo A, Barbe F, Pierola J, Pons J, Rimbau E, et al. Endothelial function and circulating endothelial progenitor cells in patients with sleep apnea syndrome. Respiration 2008;76:28–32.
[74] Murri M, Garcia-Delgado R, Alcazar-Ramirez J, Fernandez-Ramos A, Alcaide J, Cardona F, et al. Effect of CPAP on oxidative stress and circulating progenitor cell levels in sleep patients with apnea-hypopnea syndrome. Respir Care 2011;56:1830–6.
[75] Yun CH, Jung KH, Chu K, Kim SH, Ji KH, Park HK, et al. Increased circulating endothelial microparticles and carotid atherosclerosis in obstructive sleep apnea. J Clin Neurol 2010;6:89–98.
[76] Butt M, Khair OA, Dwivedi G, Shantsila A, Shantsila E, Lip GY. Myocardial perfusion by myocardial contrast echocardiography and endothelial dysfunction in obstructive sleep apnea. Hypertension 2011;58:417–24.
[77] Martin K, Stanchina M, Kouttab N, Harrington EO, Rounds S. Circulating endothelial cells and endothelial progenitor cells in obstructive sleep apnea. Lung 2008;186:145–50.
[78] Simpson PJ, Hoyos CM, Celermajer D, Liu PY, Ng MK. Effects of continuous positive airway pressure on endothelial function and circulating progenitor cells in obstructive sleep apnoea: a randomised sham-controlled study. Int J Cardiol 2013;168:2042–8.
[79] Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129–34.
[80] Chung S, Yoon IY, Lee CH, Kim JW. The effects of nasal continuous positive airway pressure on vascular functions and serum cardiovascular risk factors in obstructive sleep apnea syndrome. Sleep Breath 2011;15:71–6.
[81] Baessler A, Nadeem R, Harvey M, Madbouly E, Younus A, Sajid H, et al. Treatment for sleep apnea by continuous positive airway pressure improves levels of inflammatory markers - a meta-analysis. J Inflamm (Lond) 2013;10:13.
[82] Guo Y, Pan L, Ren D, Xie X. Impact of continuous positive airway pressure on C-reactive protein in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath 2013;17:495–503.
[83] Xie X, Pan L, Ren D, Du C, Guo Y. Effects of continuous positive airway pressure therapy on systemic inflammation in obstructive sleep apnea: a meta-analysis. Sleep Med 2013;14:1139–50.
[84] Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060–7.
[85] Bullo M, Garcia-Lorda P, Salas-Salvado J. Plasma soluble tumor necrosis factor alpha receptors and leptin levels in normal-weight and obese women: effect of adiposity and diabetes. Eur J Endocrinol 2002;146:325–31.
[86] Yue HJ, Mills PJ, Ancoli-Israel S, Loredo JS, Ziegler MG, Dimsdale JE. The roles of TNF-alpha and the soluble TNF receptor I on sleep architecture in OSA. Sleep Breath 2009;13:263–9.
[87] Kohler M, Ayers L, Pepperell JC, Packwood KL, Ferry B, Crosthwaite N, et al. Effects of continuous positive airway pressure on systemic inflammation in patients with moderate to severe obstructive sleep apnoea: a randomised controlled trial. Thorax 2009;64:67–73.
[88] Lemoine M, Serfaty L. Chronic intermittent hypoxia: a breath of fresh air in the understanding of NAFLD pathogenesis. J Hepatol 2012;56:20–2.
[89] Chin K, Nakamura T, Takahashi K, Sumi K, Ogawa Y, Masuzaki H, et al. Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. Am J Med 2003;114:370–6.
[90] Kohler M, Pepperell JC, Davies RJ, Stradling JR. Continuous positive airway pressure and liver enzymes in obstructive sleep apnoea: data from a randomized controlled trial. Respiration 2009;78:141–6.
[91] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221–31.
[92] Poynard T, Lassailly G, Diaz E, Clement K, Caiazzo R, Tordjman J, et al. Performance of biomarkers FibroTest, ActiTest, SteatoTest, and NashTest in patients with severe obesity: meta analysis of individual patient data. PLoS One 2012;7:e30325.
[93] von Kanel R, Dimsdale JE. Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease. Chest 2003;124:1956–67.
[94] von Kanel R, Natarajan L, Ancoli-Israel S, Mills PJ, Wolfson T, Gamst AC, et al. Effect of continuous positive airway pressure on day/night rhythm of prothrombotic markers in obstructive sleep apnea. Sleep Med 2013;14:58–65.
[95] Hui DS, Ko FW, Fok JP, Chan MC, Li TS, Tomlinson B, et al. The effects of nasal continuous positive airway pressure on platelet activation in obstructive sleep apnea syndrome. Chest 2004;125:1768–75.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004

[96] von Kanel R, Loredo JS, Ancoli-Israel S, Dimsdale JE. Association between sleep apnea severity and blood coagulability: treatment effects of nasal continuous positive airway pressure. Sleep Breath 2006;10:139–46.
[97] McEwen BJ, Phillips CL, Morel-Kopp MC, Yee BJ, Sullivan DR, Ward CM, et al. Diurnal changes and levels of fibrin generation are not altered by continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA). A randomised, placebo-controlled crossover study. Thromb Haemost 2012;108:701–9.
[98] Phillips CL, McEwen BJ, Morel-Kopp MC, Yee BJ, Sullivan DR, Ward CM, et al. Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. Thorax 2012;67:639–44.
[99] Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. Diabetes Care 2014;37:355–63.
[100] Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med 2014;370:2265–75.

Please cite this article in press as: Jullian-Desayes I, et al., Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.07.004